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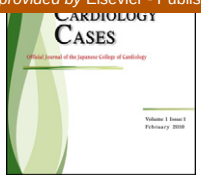

Case Report

# A case of coronary artery disease with antiphospholipid syndrome that showed repeated stent thrombosis

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**KEYWORDS**
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Acute coronary syndrome;
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**Summary** A 55-year-old man with severe chest pain was hospitalized for acute coronary syndrome. Coronary angiography revealed total occlusion of his left anterior descending coronary artery, which was successfully recanalized by percutaneous coronary intervention (PCI). However, the patient subsequently experienced subacute stent thrombosis, restenosis in the stent, and frequent thrombosis in PCI toward restenosis. Primary antiphospholipid syndrome should be considered as a possible cause of repeated stent thrombosis, and, if salvage by PCI is impossible, salvage by coronary artery bypass graft should be considered.


## Introduction

Antiphospholipid syndrome (APS) is defined clinically by the presence of recurrent arterial and venous thrombotic events as well as recurrent pregnancy loss, and serologically by a positive test for antiphospholipid antibodies (i.e. lupus anticoagulant (LA) and anticardiolipin antibodies) [1]. APS is associated with frequent and recurrent thrombosis. In the present paper, we report a case of acute coronary syndrome (ACS) with APS that showed repeated subacute stent thrombosis (SAT) after percutaneous coronary intervention (PCI) toward restenosis.

## Case presentation

A 55-year-old man had hypertension, dyslipidemia and current smoking as coronary risk factors and had been diagnosed with ACS due to coronary spasm 4 years previously. Thereafter, he had received calcium channel blocker and nicorandil.

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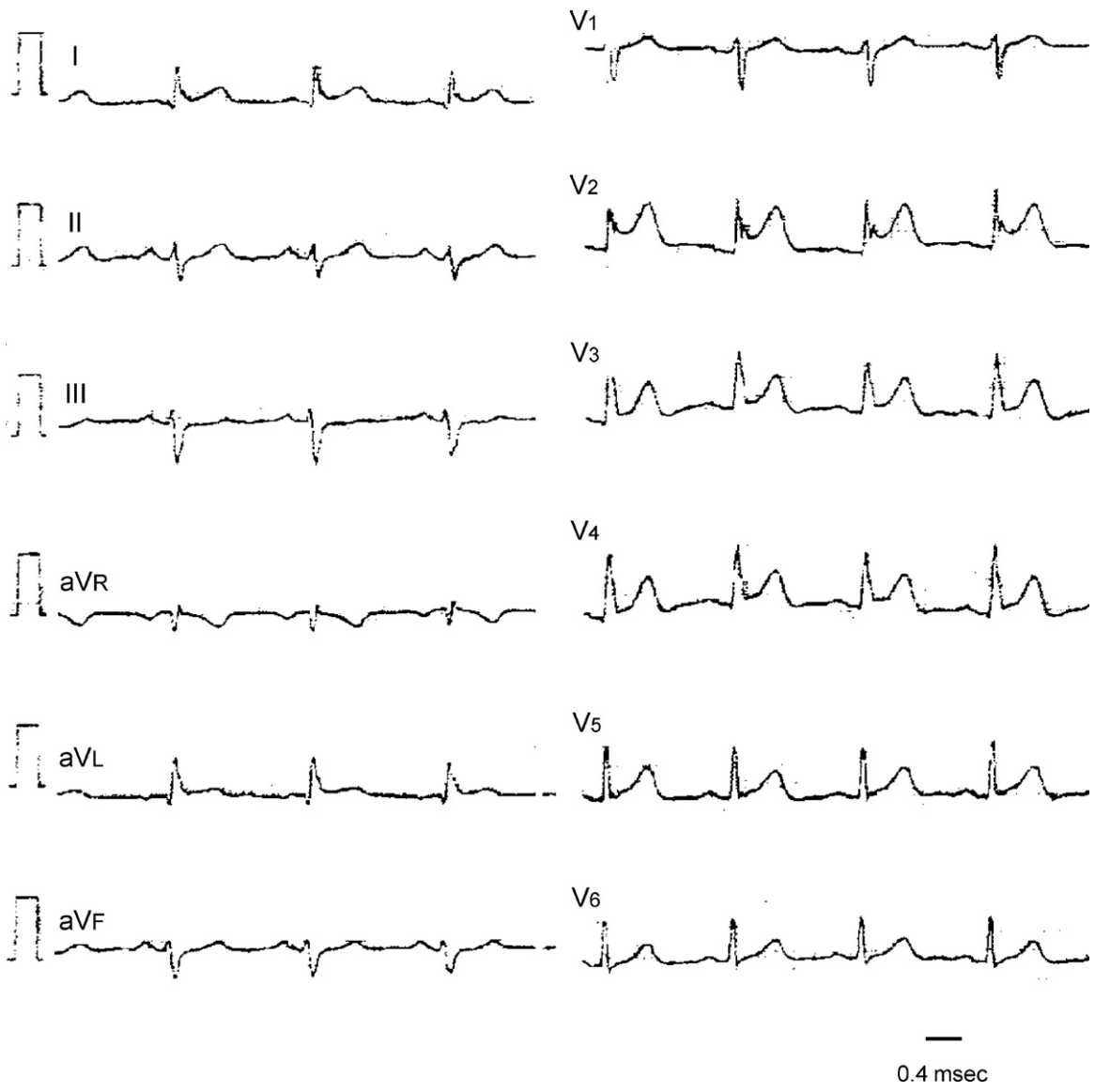


**Figure 1** Electrocardiography showed ST elevation in leads V2—V5, I and aVL.

## First hospitalization in our hospital for ACS

He visited our hospital because of sustained chest pain accompanied by cold sweat and back pain. He experienced cardiopulmonary arrest with ventricular fibrillation (Vf) soon after his arrival, and recovered to sinus rhythm with electrical defibrillation. Electrocardiography (ECG) showed ST elevation on leads V2—V5, I, and aVL (Fig. 1), and echocardiography showed hypokinesis of wall motion in the anteroseptal area. He was diagnosed with ACS and emergency coronary angiography (CAG) showed that the mid left anterior descending coronary artery (LAD) was totally occluded with thrombi (Fig. 2A). PCI including thrombectomy was performed. A bare metal stent (BMS, driver™ 3.0 mm × 24 mm) was placed across the lesion. Angiography after stent deployment showed complete expansion of the stent with grade 3 Thrombolysis In Myocardial Infarction criteria (TIMI) flow (Fig. 2B). He received oral aspirin and clopidogrel and intravenous heparin.

On hospital day 4, he again experienced chest pain and the ECG showed ST elevation in precordial leads. Emergency CAG showed that the distal edge of the stent in the mid LAD was totally occluded with thrombi (Fig. 2C). We diagnosed SAT and confirmed that stent apposition was optimal and moderate plaque remained on the distal edge of the stent as assessed by intravascular ultrasound (IVUS). A BMS (S stent™ 3.0 mm × 14 mm) was placed across this distal edge, and we added ballooning to a 2nd diagonal branch that had advanced to severe stenosis due to the plaque shift. The final angiography showed complete expansion of the stent and the 2nd diagonal branch with grade 3 TIMI flow (Fig. 2D). Since we were concerned about the insufficiency of antithrombotic therapy, we replaced heparin with intravenous argatroban, and clopidogrel with ticlopidine 200 mg/day and cilostazol 200 mg/day for antiplatelet

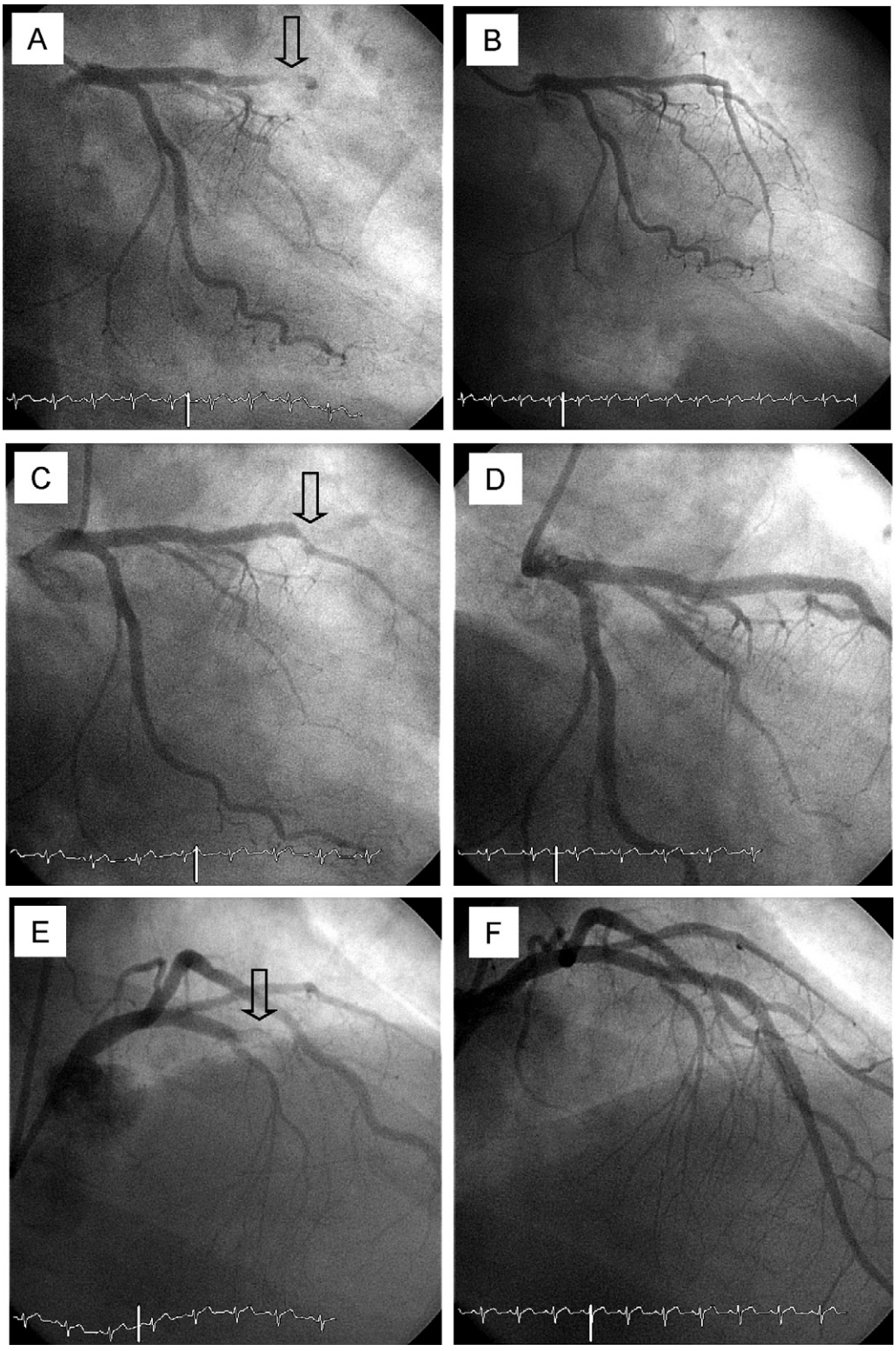


**Figure 2** Results of coronary angiography. (A) The mid left anterior descending coronary artery was totally occluded with thrombi. Arrow shows total occlusion. (B) The coronary flow in the left anterior descending coronary artery showed reperfusion by PCI. (C) The mid left anterior descending coronary artery was totally occluded with thrombi at the distal edge of the stent. Arrow shows total occlusion. (D) The coronary flow in the left anterior descending coronary artery showed reperfusion by PCI. (E) The mid left anterior descending coronary artery was totally occluded with thrombi at the proximal edge of the stent. Arrow shows total occlusion. (F) The coronary flow in the left anterior descending coronary artery showed reperfusion by PCI.

therapy, and added warfarin and bucolome for anticoagulant therapy.

However, on hospital day 5, he again experienced chest pain and the ECG showed ST elevation in precordial leads. Emergency CAG showed that the proximal edge of the stent in the mid LAD was totally occluded with thrombi (Fig. 2E). We diagnosed a recurrence of SAT, and performed PCI. Angiography after stent deployment showed LAD coronary flow with grade 3 TIMI flow (Fig. 2F). Follow-up CAG on hospital day 22 showed patency of the stent and TIMI 3 flow. On hospital day 25, he was discharged in stable general condition.

Next, we tested whether the patient was allergic to the stent materials (S-stent™, stainless steel; driver™, cobalt alloy) by a skin patch test, and he showed negative responses. A decrease in platelet values that would have suggested heparin-induced thrombocytopenia (HIT) was not observed. Moreover, we measured platelet aggregability, with adenosine 5-diphosphate and collagen as agonists. Consequently, aggregation in response to both agonists was inhibited. After discharge, we measured platelet aggregability on aspirin 100 mg/day and ticlopidine 200 mg/day for antiplatelet therapy, and aggregation in response to both agonists was again inhibited. The values of protein-S, protein-C, antithrombin III, antinuclear antibody and others were within normal limits. We also measured anti-cardiolipin $\beta_2$-glycoprotein I complex antibody (anti-CL$\beta_2$ GPI-antibody) and LA, and considered the possibility of APS. Consequently, the titer of anti-CL$\beta_2$ GPI-antibody was below a moderate value (99 percentile) that could satisfy the laboratory criteria for APS [2], but LA was positive (anti-CL$\beta_2$ GPI-antibody 5.0 U/ml, LA 1.54). To satisfy the standard laboratory criteria for APS, we measured LA after discharge and it was again positive for LA (2.43 and 1.94). However, we could not exclude the possibility that LA after discharge was a false-positive, since the administration of warfarin can give a false-positive for LA [3]. While LA was initially measured before the administration of warfarin, LA was measured after the administration of warfarin in the 2nd and 3rd tests. In addition, systemic thrombosis for APS showed an atypical pattern of ''stent thrombosis''.

We discontinued warfarin 3 months after the 1st discharge, and we had identified that platelet aggregability could be significantly inhibited by other antithrombotic therapy (aspirin, ticlopidine and cilostazol).

## Second hospitalization for post-infarction angina

Four months after the 1st discharge, he was admitted to our hospital again because of chest discomfort. We suspected post-infarction angina, and CAG showed 75% in-stent restenosis in the mid LAD and 90% stenosis in an ostial lesion of the 2nd diagonal branch, and other coronary arteries did not show any significant change (Fig. 3A). We diagnosed that restenosis was the culprit lesion of post-infarction angina. We performed plane old balloon angioplasty (POBA) on the in-stent restenosis (ISR) lesion, and identified sufficient expansion of the lesion, but also identified haziness in the lesion (Fig. 3B). We applied POBA to the lesion again, and haziness in the lesion disappeared. However, thrombosis appeared in the ostium of the 2nd diagonal branch and distal LAD (Fig. 3C). We aspirated in the LAD with a thrombus aspiration catheter, and the thrombus in the 2nd diagonal branch disappeared, while we noted total occlusion of the distal LAD and recurrence of the above-mentioned haziness in the stent (Fig. 3D). Due to concerns about the possibility of HIT, we discontinued the administration of intravenous heparin and started the administration of intravenous argatroban. Thereafter, we repeated POBA, aspiration of thrombus and forceful injection, and observed almost complete disappearance of the haziness in the stent, but the total occlusion in the distal LAD and 2nd diagonal branch remained (Fig. 3E and F). We maintained the activated coagulation time (ACT) longer than 250 s, and a decrease in platelet values that would have suggested HIT was not observed. In addition, a test for HIT antibody was negative.

## Third hospitalization in our hospital for post-infarction angina

Two months after the 2nd discharge, the patient was again admitted to our hospital due to a recurrence of chest pain. We performed elective, which showed in-stent total occlusion in the mid LAD, the restoration of coronary flow in the 2nd diagonal branch, and the development of collateral circulation (Rentrop classification 2) from the 2nd diagonal branch to the distal LAD (Fig. 4A and B). He again showed a positive test for LA without the administration of warfarin, and consequently was diagnosed as APS with frequent thrombosis. If he was treated by PCI, the lesion was indicated for a drug-eluting stent (DES). However, in consolidating APS, the use of a DES may induce more frequent stent thrombosis than the use of a BMS [4]. Based on the previous episode of thrombosis with the PCI technique, we judged that coronary artery bypass graft (CABG) was appropriate. He received off-pump CABG (left internal thoracic artery — LAD, right internal thoracic artery — 2nd diagonal branch). During and after the operation, there were no significant complications. The administration of warfarin was restarted after the operation. We confirmed that the bypass grafts were patent by coronary CT, and he was discharged on the 6th post-operative day.

## Discussion

We have reported an uncommon case of CAD with APS, involving 2 occurrences of in-stent thrombosis in a patient with ACS within 48 h, which included frequent thrombosis in PCI, and total in-stent occlusion, which was contra-indicated for PCI.

Schomig et al. reported that the frequency of in-stent thrombosis was 0.8% [5], Leon et al. reported a value of 0.6% [6], and the j-Cypher Registry gave values of 0.47% within 30 days, 0.74% within 1 year and 0.94% within 2 years [7]. Thus, the frequency of in-stent thrombosis appears to be less than 1.0%. On the other hand, many predictors of stent thrombosis have been identified, such as under-expansion of the stent, discontinuation of antiplatelet therapy, insufficiency of and resistance to antithrombotic therapy, ACS, residual dissection, HIT, platelet activation due to operational invasion, diabetes mellitus and renal failure. In

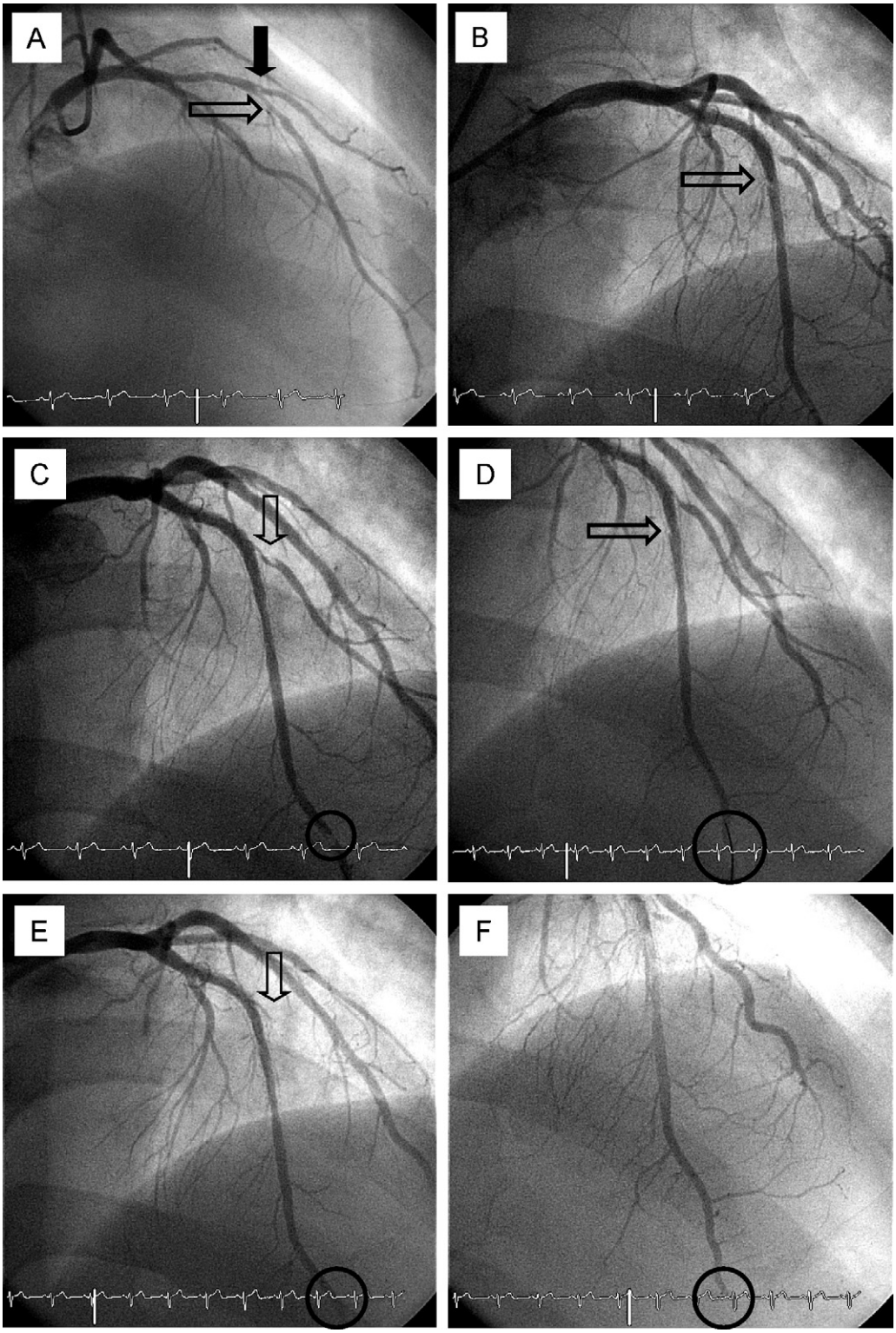


**Figure 3** (A) Coronary angiography showed 75% in-stent restenosis in the mid LAD and 90% stenosis in an ostial lesion of the 2nd diagonal branch. The transparent arrow shows in-stent restenosis in the LAD. The black arrow shows stenosis in the 2nd diagonal branch. (B) Coronary angiography after POBA of the ISR lesion showed haziness in the stent. The arrow indicates haze. (C) Coronary angiography after POBA of the hazy lesion showed the disappearance of haziness and the appearance of thrombosis in the ostium of the 2nd diagonal branch and distal LAD. The arrow shows thrombi in the 2nd diagonal branch. The circle shows thrombi in the distal LAD. (D) Coronary angiography after thrombus aspiration shows the disappearance of the thrombus in the 2nd diagonal branch, total occlusion of the distal LAD, and the recurrence of haziness in the stent. The arrow shows haziness. The circle shows thrombi in the distal LAD. (E) Final coronary angiography shows the disappearance of haziness in the stent, and total occlusion in the distal LAD (circle) and 2nd diagonal branch (arrow). (F) Final coronary angiography shows total occlusion in the distal LAD (circle).

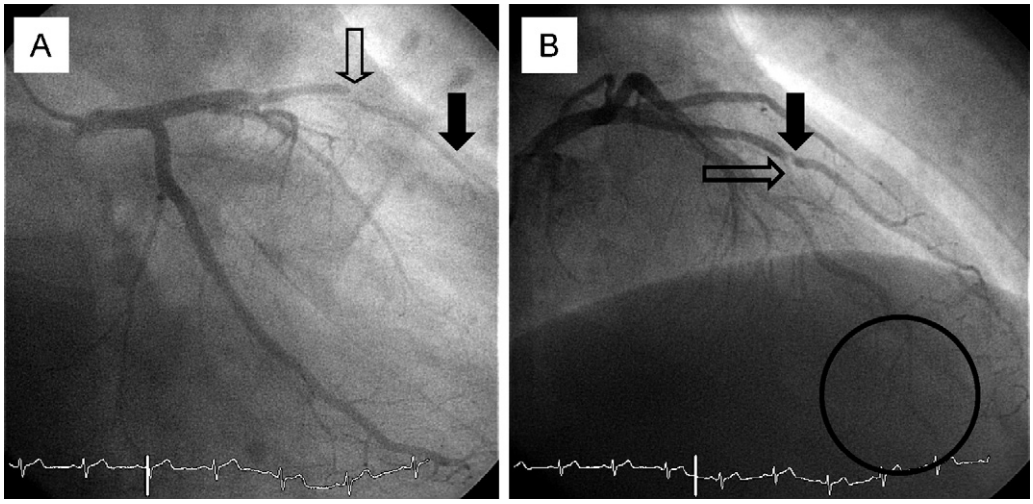


**Figure 4** (A) Coronary angiography shows total occlusion in the stent in the mid LAD (transparent arrow) and the restoration of coronary flow in the 2nd diagonal branch (black arrow). (B) Coronary angiography shows in-stent total occlusion in the mid LAD (transparent arrow), the restoration of coronary flow and ostial 90% stenosis in the 2nd diagonal branch (black arrow), and the development of collateral circulation (Rentrop classification 2) from the 2nd diagonal branch to the distal LAD (circle).

addition, predictors of frequent thrombosis in PCI have been identified, such as HIT, resistance to and insufficiency of antithrombotic therapy, and the inability to prolong the ACT in PCI.

In this case, just after PCI for ACS, the administration of heparin did not prolong the activated partial thromboplastin time (aPTT). First, SAT occurred, and therefore we initially suspected a heparin insufficiency. Thereafter, we replaced heparin with argatroban and prolonged the therapeutic range of aPTT, but a 2nd incidence of SAT occurred. We could not explain this thrombosis solely based on the insufficient prolongation of aPTT. Moreover, the later thrombosis and occlusion in the stent occurred under a sufficient antiplatelet effect, stent apposition, prolonged ACT and aPTT in PCI, and negative HIT. Therefore, we could not initially explain his clinical course.

## Diagnosis of APS

In this case, we diagnosed APS at the 3rd admission. When we considered the actual classification criteria [2], his data were consistent with the clinical criteria ''Arterial, venous or small vessel thrombosis in any tissue or organ, to be confirmed by objective validated criteria'' and the laboratory criteria ''Lupus anticoagulant present in plasma''.

In this case, thrombosis only occurred in the stent and the branch near the lesion, and did not occur in other vessels. Therefore, we did not suspect that thrombosis was caused by APS. Moreover, since the patient had received warfarin for a while, we did not closely examine whether the results of the follow-up LA test were actually a false-positive. Our diagnosis of APS may have been delayed due to this confusion.

## Thrombosis in PCI

With regard to the stent thrombosis at the 1st admission, it has been reported that antiphospholipid antibody may contribute to early stent occlusion [8]. In particular, it has been reported that patients with coronary artery sclerosis with systemic lupus erythematosus (SLE) and positive antiphospholipid antibody with a DES frequently showed thrombotic occlusion in their stents. The presence of antiphospholipid antibody and the delayed formation of neo-intima by DES had also been discussed [4].

With regard to total occlusion in the stent at the 3rd admission, we suspected that this was more likely a case of subacute occlusion than acute occlusion based on the symptomatic course and the development of collaterals. Occlusion occurred where we had identified the previous ISR and the formation of thrombus at the 2nd admission. We suspected that re-restenosis was due to both the proliferation of intima and the formation of thrombus. The antiproliferative effect of antiphospholipid antibody on intima in the stent has been reported to both promote atherosclerosis [9] and suppress atherosclerosis [10], and thus this point is controversial. Therefore, we could not conclude whether APS was associated with the repeated ISR. Since coronary risk factors were adequately controlled and the patient continued to take his medication after the onset of AMI, we could not identify a possible cause of repeated ISR in such a short period except for APS.

## Treatment of CAD with APS

The algorithm for the treatment of APS reported by Lim et al. is very useful because it is based on the presently available evidence [11]. In a case of recurrent thrombosis, this algorithm recommends treatment consisting of ''Low-Molecular-Weight-Heparin or Unfractionated Heparin or Warfarin With a Higher Target INR (INR > 3.0) or Warfarin Plus Antiplatelet Agent.'' In this case, the events occurred during periods of insufficient or no administration of warfarin. It is possible that none of these events may have occurred if the patient had received sufficient warfarin.

Therefore, we should reconsider the role of warfarin in the development of APS.

In cases of CAD with APS that require revascularization, we waver between PCI and CABG. Both techniques have been reported to fail in association with thrombosis [8,12]. To date, there are few case reports and there are no established guidelines regarding the method for revascularization. In particular, we should avoid the use of DES in cases of PCI [4]. We hope that treatment guidelines can be established in the future, based on a consideration of cases such as this.

Finally, this case raises some significant points for the management of CAD with APS. We should be aware of the role that the administration of warfarin plays in APS and should choose CABG in cases that are contra-indicated for PCI.

## References

[1] Cervera R, Espinosa G. Antiphospholipid syndrome: long-time research on pathogenic mechanisms has finally led to new therapeutic strategies. Expert Opin Ther Targets 2010;14:1279—82.

[2] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, Groot DE, Koike PG, Meroni T, Reber PL, Shoenfeld G, Tincani Y, Vlachoyiannopoulos A, Krilis PGSA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295—306.

[3] Armando T, Veena C, Marigrazia C, Pier MM. Laboratory diagnosis of lupus anticoagulants for patients on oral anticoagulant treatment. Thromb Haemost 2002;88:583—6.

[4] Lee CH, Chan MY. Dilemma of drug-eluting stent implantation in a patient with systemic lupus erythematosus. Int J Cardiol 2007;114:e107—8.

[5] Schömig A, Kastrati A, Mudra H, Blasini R, Schühlen H, Klauss V, Richardt G, Neumann FJ. Four-year experience with Palmaz-Schatz stenting in coronary angioplasty complicated by dissection with threatened or present vessel closure. Circulation 1994;90:2716—24.

[6] Leon L, Baim MB, Popma DS, Gordon JJ, Cutlip PC, Ho DE, Giambartolomei KK, Diver A, Lasorda DJ, Williams DM, Pocock DO, Kuntz SJRE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998;3(39):1665—71.

[7] Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H, Nishikawa H, Hiasa Y, Muramatsu T, Meguro T, Inoue N, Honda H, Hayashi Y, Miyazaki S, Oshima S, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation 2009;119:987—95.

[8] Chambers Jr JD, Haire HD, Deligonul U. Multiple early percutaneous transluminal coronary angioplasty failures related to lupus anticoagulant. Am Heart J 1996;32:189—90.

[9] Nicolo D, Monestier M. Antiphospholipid antibodies and atherosclerosis. Clin Immunol 2004;112:183—9.

[10] Nicolo D, Goldman BI, Monestier M. Reduction of atherosclerosis in low density lipoprotein receptor-deficient mice by passive administration of antiphospholipid antibody. Arthritis Rheum 2003;48:2974—8.

[11] Cervera C, Piette R, Font JC, Khamashta J, Shoenfeld MA, Camps Y, Jacobsen MT, Lakos S, Tincani G, Kontopoulou-Griva A, Galeazzi I, Meroni M, Derksen PL, de Groot RH, Gromnica-Ihle PG, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1000 patients. Arthritis Rheum 2002;46:1019—27.

[12] Parwis M, Surreya MC, Matthias T, Kienbaum P, Jarowit A, Gunter M, Christof S, Heinz J. Antiphospholipid syndrome in cardiac surgery-an underestimated coagulation disorder? Eur J Cardio-Thorac Surg 2005;28:133—7.